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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,442	06/11/2001	Vincent Dubois	MXI-321CP	3549

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EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,442	DUBOIS ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-21,23-30,37,38 and 118-124* is/are pending in the application.

4a) Of the above claim(s) *10,18-21,23,27,29 and 121-124* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9,11-17,25,26,30,37,38 and 118* is/are rejected.

7)☒ Claim(s) *28,119 and 120* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5-21, 23-30, 37, 38, and 118-124 are pending, with claims 4, 22, 31-36, and 39-117 are cancelled, and presented new claims 121-124, according to the response filed May 4, 2005.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

Any rejection or objection not specifically addressed is herein withdrawn.

Applicant's amendment to the specification is acknowledged, amending the claim of priority.

Applicant's arguments/amendments, filed May 4, 2005, with respect to claims 1-3, 5-21, 23-30, 37, 38, and 118-124 have been fully considered and are persuasive. The rejection of claims 1-3, 5-21, 23-30, 37, 38, and 118-124 has been withdrawn, as the prior art does not read upon the amended claims, with respect to the elected species succinyl-βAla-Leu-Ala-Leu-Ala-Dox. In view of the amendments to the claims, the Examiner agrees with Applicant's arguments that it would not have been obvious to succinylate the βAla-Leu-Ala-Leu-Ala-Dox peptide conjugate and expect the reduced toxicity observed.

Applicant's elected species, succinyl-βAla-Leu-Ala-Leu-Ala-Dox is thus found to be free of the art. It is noted that claims 119 and 120 would be found allowable if written in independent form, as set forth at the end of this office action.

The Examiner has extended the search to the species of claim 28, from which claim 119 depends. The species succinyl-βAla-Leu-Ala-Leu-Ala-Dnr and glutaryl-βAla-Leu-Ala-Leu-Ala-

Dox have been found to be free of the art. It is noted that claim 28 would be found allowable if written in independent form, as set forth at the end of this office action.

The Examiner has extended the search to the following species, PEG-βAla-Leu-Ala-Leu-Ala-Dox, as readable upon the (stabilizing group)-βAla-Leu-Ala-Leu-Ala-Dox. PEG is a neutral group. The Examiner is unable to determine if new claims 121-124 are readable upon the species. The Examiner has determined the species to be readable upon claims 1-3, 5-9, 11-17, 25, 26, 30, 37, 38, and 118.

Claims 10, 18-21, 23, 24, 27, 29, and 121-124 have been withdrawn as not readable upon the species PEG-βAla-Leu-Ala-Leu-Ala-Dox, or have not been indicated as allowable but objected to (claims 28, 119, and 120, *see Allowable Subject Matter below*).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-9, 11-17, 25, 26, 28, 37, 38, and 118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107

> F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a

method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

In the instant case, the claims are drawn to a compound comprising: a therapeutic agent 'capable of entering a target cell', an oligopeptide (4-20 aa in length), a negatively charged or neutral stabilizing group, and an optional TOP-cleavage resistant linker group. The compound is (stabilizing group)-(oligopeptide)-(optional linker)-(therapeutic agent). The stabilizing group must reduce *in vivo* acute toxicity of the compound and the compound must be cleavable by 'an enzyme associated with the target cell'.

(1) Level of skill and knowledge in the art:

The level of skill and knowledge of the artisan is high, with regards to drug synthesis.

(2) Partial structure:

The oligopeptide must have 1 non-genetically encoded amino acid positioned 4 residues from the therapeutic agent.

The specification and claims provide for a variety of therapeutic agents which are anticancer agents. The specification and claims do not provide sufficient variety in structure to describe all therapeutic agents 'capable of entering a target cell' which are not used in cancer therapy.

The specification and claims provide for oligopeptides of SEQ ID NOs: 1-103. The specification and claims do not provide sufficient variety of oligopeptides embraced by the generic claim, including examples of any oligopeptides where n >3.

The specification and claims provide examples of negatively charged and esterified dicarboxylic acids as the stabilizing group. The claims and specification are silent to the myriad of compounds embraced by neutral stabilizing group, beyond the esterified dicarboxylic acids, and do not provide sufficient variety of 'stabilizing groups that reduce acute toxicity when administered *in vivo*'.

The specification and claims provides for the target-cell-associated enzyme to be TOP. The specification provides for the target-cell to be a colorectal, cervical, or breast cancer cells. The specification and claims do not provide sufficient variety to describe the myriad of target cells other than the three types of cancer cells, nor does the specification provide for any examples to describe a non-TOP enzyme associated with a target cell.

Thus, the specification fails to provide sufficient variety to describe the myriad of compounds embraced by the generic claims.

(3) Physical and/or chemical properties:

The backbone must be of the general formula (stabilizing group)-(oligopeptide)-(optional linker)-(therapeutic agent).

The stabilizing group must be negatively or neutrally charged.

(4) Functional characteristics:

The compound must have a reduced *in vivo* acute toxicity and must be cleavable by an enzyme associated with the cell.

The therapeutic agent must be capable of entering a target cell.

(5) Method of making the claimed invention:

The specification provides description for the synthesis of succinyl-βAla-Leu-Ala-Leu-Dox. Peptide synthesis and coupling drug-peptide conjugates are routine techniques in the art.

The specification does not provide sufficient variety in making compounds with the asserted biological activity, e.g., having reduced acute *in vivo* toxicity, and being cleavable by an enzyme associated with a target cell.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 1-3, 5-9, 11-17, 25, 26, 30, 37, 38, and 118 are broad generic claims, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of compounds which would have the alleged activity at cells other than the colorectal, cervical, or breast cancer cells. While having written description of the compounds of claim 28, and compounds identified in the specification tables and/or examples, the specification is void of sufficient variety of compounds that qualify for the functional characteristics claimed.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

Claims 1-3, 5-9, 11-17, 25, 26, 30, and 118 are rejected under 35 U.S.C. 103(a) as being unpatentable over TROUET and Baurain (US Patent 5,962,216, cited in previous Office Action), in view of VERONESE (US Patent 5,286,637), DALBORG (US Patent 6,048,720), GAERTNER (H.F. Gaertner and R.E. Offord. Bioconj. Chem. (1996) 7(1), pages 38-44), and INADA (Y. Inada, et al. Methods Enzymol. (1994) 242, pages 65-90).

The instant claims are described *supra*.

Trouet teaches the conjugate βAla-Leu-Ala-Leu-Ala-Dox (SEQ ID NO:2, sequence listing and, e.g., column 7, line 37: *describing Fig. 30*). Dox is a therapeutic capable of entering a cell, the tetrapeptide βAla-Leu-Ala-Leu-Ala is cleavable by TOP. Trouet does not teach PEGylated βAla-Leu-Ala-Leu-Ala-Dox. PEG is considered a neutral stabilizing group.

Gaertner teaches that, "Covalent attachment of monomethoxypoly(ethylene glycol) [mPEG] to therapeutic proteins prolongs their circulatory life time *in vivo*, reduces their antigenicity and immunogenicity, and improves their resistance to proteolysis. These properties

are of great clinical interest, especially in the case of relatively small proteins, where it is believed that an increase of the Stoke's radius is consistent with a reduced renal clearance." (citations removed, page 38).

Veronese teaches that, "Modification of biologically active substances such as peptide or proteins with [mPEG] is reported to change extensively their physical, chemical, enzymological, immunological, as well as their pharmacological and pharmacokinetic properties." (column 1, lines 15-19).

Veronese teaches that, "Such modified peptide or protein derivatives exhibit some advantages when compared to the peptide or protein itself: increased water solubility, decreased antigenicity or increased half-life of the circulating peptide or protein." (column 1, lines 24-28).

Veronese teaches that, "It may have been found that some, if not all of the above mentioned drawbacks [difficulty incorporating radioactive probe, inactivation of enzyme, difficulty modulating cleavage, and difficulty introducing targeting sequences into the polymer-conjugate] can be eliminated or at least significantly reduced by making use of the new drug polymer derivatives of the invention which are represented by the generic formula RO-$(CH_2CH_2O)_n$-(CO)-NH-X-(CO)-NH-Z" where R is a lower alkyl, n is between 25 and 500, NH-X-(CO) is an amino acid, or a di- or tri-peptide, NH-Z is either a biologically active peptide or NH_2, and (CO)-N represents a peptide bond (column 1, lines 41-58).

Preferred species R is a methyl, n is between 40 and 115 (e.g., molecular weights between 1800 and 5500). (column 1, line 59-64). NH-Z represents a peptide, protein or drug (column 2, line 4)

Dalborg teaches that, "It is well known, that the in-vitro stability and in-vivo half-life of polypeptides can be increase by covalently attachment of biocompatible polymers (in the following referred to as conjugation or modification). Modification of the polypeptide surface also has the advantage of decreasing immunogenicity exhibited by the polypeptide." (column 1, line 23+).

Dalborg further teaches that, "Pegylation, i.e. coupling of various [PEG] to a polypeptide, is a technique widely used for increasing the in-vitro stability and in-vivo half-life of e.g. proteins. In pegylation, many techniques have been proposed of the years." (column 1, line 30+).

Inada teaches that, "enzymes modified with a [PEG] derivative become more soluble and remain active in organic solvents. Because PEG is an amphipathic macromolecule, its hydrophilic nature makes it possible to modify enzymes in aqueous solution, and its hydrophobic nature would make modified enzymes soluble in hydrophobic environments. In fact, modified enzymes such as catalase and peroxidase have markedly high activities in organic solvents." (page 71).

Inada teaches, "The effect of the modification with [PEG] on the reduction of immunoreactivity depends on the molecular weight of the [PEG], the degree of modification of amino groups, and the shape of the modifiers (chain form or comb form). If the average molecular weight of [PEG] is lower than 5000, serious reduction in the enzymatic activity results without complete elimination of immunoreactivity. Therefore, [PEG] with a molecular weight of more than 5000 is recommended as a modifier." (page 87, discussed with regards to Asparaginase activity).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have PEGylated the βAla-Leu-Ala-Leu-Ala-Dox peptide conjugate, because mPEG increases the biological half-life and retain the biological activity of the peptides to which they are attached, as taught by Johnston, Dalborg, and Gaertner.

One would have been motivated to make the PEGylated βAla-Leu-Ala-Leu-Ala-Dox peptide conjugate for the benefit of increasing solubility in both aqueous and organic solvents, increasing the half-life and clearance time, reducing both antigenicity and immunogenicity, and improving the resistance to proteolysis, while retaining biological activity of the βAla-Leu-Ala-Leu-Ala-Dox peptide conjugate.

One of ordinary skill in the art would have had a reasonable expectation for success in making the PEGylated βAla-Leu-Ala-Leu-Ala-Dox peptide conjugate, as PEGylation of peptides is a routine technique widely practiced in the peptide arts for the reasons stated *supra*, as taught by Johnston, Dalborg, Gaertner, Inada, and Veronese.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Allowable Subject Matter

Claims 28, 119, and 120 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-097474. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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